REMARKS

In view of the foregoing amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Following the Gulf war, a number of US combatants reported neurological symptoms of unknown etiology (Gulf War Syndrome). Simultaneous exposure to chemicals used has been implicated as a factor in the neurotoxicity. The chemicals used included pyridostigmine, permethrine, and DEET (N,N-diethyl-m-toluamide). It is in this light that significant research efforts have been focused not only on determining the cause of the Gulf War Syndrome, but also on improving the safety of insect repellents. Ideally an insect repellent possesses prolonged repellency towards a selected species of insect without appreciable absorption by the user.

DEET is a broad spectrum repellent that is effective against mosquitoes, biting flies, and ticks. The latest reports show that DEET still remains the standard of currently available insect repellents. It is estimated that more than 38% of the American population uses DEET based repellents, with a world wide use estimated at over 2 million people yearly.

DEET is available in multiple topical formulations including solutions, lotions, creams, gels, aerosols, impregnated towellettes, and pump sprays, with concentrations ranging from 5 to 100%, and varying durations of action. Commercial products in the market are typically formulated in ethyl alcohol or isopropyl alcohol.

Even though it has been used for over 40 years, there has been a growing interest in the safety of DEET, and as a result, an increase in the number of absorptive studies done in man and other animals. Several studies have looked at DEET's ability to enhance dermal delivery of certain drugs. These studies suggest that DEET may be a permeation enhancer. Due to its lipophilicity, DEET is prone to absorption through the skin after topical use, especially when high concentrations are used in pediatric populations. Toxicity of an agent is related to its concentration at the site of action. Therefore the rates of absorption, distribution, biotransformation, and excretion will significantly influence the toxic response exerted by DEET. Variability in absorption among individuals may depend, among other things, on the lipid content of the skin, the size of the dose given, and other drugs that are concomitantly administered along with DEET. Approximately 17% of the dose administered topically is absorbed within two hours of administration. The toxicity of DEET related to this attribute has been a subject of continued research. Several studies have looked into reducing the topical absorption of DEET without compromising the duration of its effectiveness.

Metabolic biotransformation results in detoxification of DEET by cytochrome p450 and plasma hydrolyzing enzymes. DEET is completely metabolized and several metabolites have been characterized. The major metabolites identified as ethyltoluamide and N,N-diethyl m-hydroxymethylbenzamide have been detected using both *in vitro* and human studies. However, when very large doses are given, studies show that a significant portion of the dose is excreted unchanged in the urine.

Urinary excretion accounts for nearly all of the dermally absorbed dose of DEET. It is excreted as metabolites, mainly as conjugates. Almost 90% of the absorbed dose can be recovered in the urine 24 hours after administration of the last dose.

Toxicity reports of great concern in the general population involve encephalopathy, over 90% of which were in children younger than 8 years. Along with the neurological effects seen with the Gulf War Syndrome, this makes the central nervous system (CNS) the major site of toxicity. Ingestion of large doses of DEET can produce seizures and coma by direct action on the CNS. DEET crosses the blood brain barrier, and simultaneous exposure with agents that inhibit its metabolism will indirectly increase concentrations that will ultimately cross the blood brain barrier. This has been offered as a likely explanation for the adverse interaction when DEET is used simultaneously with pyridostigmine and permethrine.

Studies of the pharmacokinetics of DEET, and comparisons of its transdermal absorption in different formulations have been carried out.

However, there continues to be a need for an improved formulation of DEET having reduced absorption through the skin, and/or extended duration of protection.

Applicants acknowledge the objection raised by the U.S. Patent and Trademark Office ("PTO") with respect to the use of the abbreviation "IPA" in the specification. "IPA" is an abbreviation for "isopropyl alcohol," as set forth on page 17, lines 1-2 of the specification. The objection to the use of the abbreviation "IPA" should therefore be withdrawn.

The PTO has requested that applicants provide dates for references not initialed on the March 15, 2002, information disclosure statement. Accordingly, applicants have submitted herewith a Supplemental Information Disclosure Statement providing dates for each of the non-initialed foreign patent references. Additionally, applicants have corrected International Publication Number from "WO 07/31709" to "WO 97/31709" and have deleted the references JP 318,429, JP 084,993, and JP 294,597, which are duplicates of JP 07173022, JP 63250309, and JP 07126120, respectively.

The rejection of claims 22-24, and 26-31 under 35 U.S.C. § 102(b) as being anticipated by Matome, "DEET Incorporation Onto HDTMA Treated BP Clay: A Basis for DEET Formulation with Decreased Percutaneous Absorption," Thesis submitted to SUNY Buffalo (catalogued October 19, 1999) ("Matome") is respectfully traversed.

In particular, Matome does not qualify as Section 102(b) prior art. More specifically, as set forth in an e-mail from the Central Technical Services and Health Sciences Library at the State University of New York at Buffalo, attached hereto as Exhibit A, Matome was published in October of 1998. In particular, Matome was first catalogued on October 19, 1999 and later catalogued in the Health Sciences Library at the State University of New York at Buffalo and shelved on November 2, 1999 (Exhibit A). As set forth in Manual of Patent Examining Procedures §§ 2128 and 2128.01, a thesis placed in a university library may be prior art if sufficiently accessible to the public. (MPEP §§ 2128.01). "A doctoral thesis indexed and shelved in a library is sufficiently accessible to the public to constitute prior art as a 'printed publication.'" (emphasis added) (citing In re Hall, 781 F.2d 897, 228 USPQ 453 (Fed. Cir. 1986)). Id. The present application was filed on October 18, 2001 and claims priority benefit to U.S. Provisional Application Serial No. 60/241,398, filed October 18, 2000. The invention of claims 22-32 was originally disclosed in U.S. Provisional Application Serial No. 60/241,398 ('398 application) (see e.g., claims 21-30 of the '398 application), and is, therefore, entitled to the benefit of that application's filing date of October 18, 2000. Since Matome was made available to the public at the earliest on October 19, 1999, less than a year before the present application's earliest filing date, Matome cannot qualify as Section 102(b) prior art.

Moreover, Matome is not available as 102(a) art, in view of the Declaration of Paul Kostyniak and Ross Giese Under 37 C.F.R. § 1.132 submitted herewith ("Declaration"). As demonstrated in the Declaration, Matome is not prior art under 35 U.S.C. § 102(a). The present invention was conceived solely by Paul Kostyniak and Ross Giese (Declaration ¶ 3). Further, Matshediso Matome, did not contribute to the conception of the present invention (Declaration ¶¶ 4). Matshediso Matome was a graduate student who was working in the laboratory of Paul Kostyniak at the time Matome was prepared (Id.). At that time, Matshediso Matome performed experiments as described in Matome at the direction of and under the supervision of Paul Kostyniak and Ross Giese (Id.). The results of these experiments were included in Matome and submitted to the Faculty of the Graduate School of the State University of New York at Buffalo in partial fulfillment of the requirements for the degree of Master of Arts by Matshediso Matome (Id.). Matshediso Matome did not

contribute to the conception of the invention as described and claimed in the above-identified application (Id.). In view of the Declaration, it is clear that Matome is not the work of "another", under 35 U.S.C. § 102(a). See In re Katz, 687 F.2d 450, 215 USPQ 14 (C.C.P.A. 1982). As a result, Matome cannot be Section 102(a) prior art with respect to the claimed invention, and the rejection based on this reference should be withdrawn.

The rejection of claims 2-24, and 26-32 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,346,922 to Beldock et al ("Beldock") in view of Matome is respectfully traversed in view of the above amendments and remarks.

As described above, Matome is not available as prior art against the present application. Accordingly, the rejection based on Beldock in view of Matome is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: August 18, 2003

Georgia Evans
Registration No. 44,597

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1672
Facsimile: (585) 263-1600

Evans, Georgia

From: Dean, Linda
Sent: Thursday, July 10, 2003 1:55 PM
To: Evans, Georgia
Subject: Date of Masters Thesis

Georgia,

Here is the written information from UB. Do you have a billing number? Thanks.

Linda

-----Original Message-----
From: smyer@acsu.buffalo.edu [mailto:smyer@acsu.buffalo.edu]
Sent: Thursday, July 10, 2003 1:04 PM
To: Dean, Linda
Subject: Re: FW: Date of Masters Thesis

Hi Linda,

Here is the information that you requested:

According to our records, the thesis, "Deet Incorporation onto HDTMA Treated BP Clay: A Basis for Deet Formulation with Decreased Percutaneous Absorption," by Matshediso Matome, was cataloged by our Central Technical Services staff on October 19, 1999, and sent to the Archives. On that date, the catalogue data was added to the OCLC system. The Health Sciences Library catalogued the thesis on November 2, 1999, and it was shelved in the stacks with the other theses.

If there are any further questions, please don't hesitate to ask.

Shelley

Shelley Myer
Visiting Senior Assistant Librarian
Central Technical Services and Health Sciences Library
SUNY University at Buffalo
smyer@buffalo.edu